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A modular fuzzy expert system for chemotherapy drug dose scheduling

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ABSTRACT

This study presents a modular Fuzzy Expert System (FES) for chemotherapy drug dose scheduling. The computational model considers the patient's Body Surface Area (BSA) and experts' opinions to calculate chemo doses following the clinical practice. A proper balance between reducing cancerous cells and toxic side effects is required for effective drug scheduling. Still, in many cases, traditional clinical approaches fail to determine appropriate therapeutical doses that balance all restrictions. In our proposed system, FES-1 is developed to determine primary drug doses based on experts' opinions and competing treatment objectives. To adjust the dose, FES-2 is developed based on clinical practices, the patient's BSA, and experts' opinions. The final chemotherapy drug dose schedule is generated by combining the outputs of FES-1 and FES-2, which is the proposed modular FES. A growth model is used in this work to observe response due to administration of chemotherapy drug doses and to determine the following doses by considering cancer patients' three weight patterns (increasing, decreasing, and random order). Extensive simulation results and comparative assessment with other current computational chemotherapy drug scheduling models validate the effectiveness and the superiority of the model proposed in this study over the other methods reported in relevant studies.

1. Introduction

Cancer is a disease of malignant cells that interact with and co-operate with their surroundings in complex ways, stimulating tumor (i.e. cancerous area) growth, while preventing the development of new blood vessels [1]. Some types of cancer do not form a tumor such as leukemias, myeloma and most types of lymphoma, which are not the focus of this research. There are four major approaches to cancer treatment: surgery, radiotherapy, bio-therapy with agents and chemotherapy [2]. Surgery and radiotherapy are local treatments. Bio-therapy with agents uses biological agents (such as hormones, antibodies and growth factors) to treat cancer regardless of the location [3,4]. Chemotherapy is an effective cancer treatment by applying drugs into human body that destroys cancer cells [2,5]. The key characteristics of cancer is the cell division that happens quickly. Chemotherapeutic drugs are applied at the time of cell division. Chemotherapy affects other living cells fast under usual conditions, such as those in the bone marrow, digestive system, and hair follicles, because it is unable to discriminate normal cells from cancerous ones [3,4,6]. As a result, common adverse effects of chemotherapy include extreme tiredness, pain in muscles, myelosuppression (lower blood cell formation, resulting in immunosuppression), mucostisitis (inflammation of the digestion lining), and hair loss (baldness) [3,4,6,7]. There are different classes of drugs such as alkylating agents, antimetabolites, anthracyclines and topoisomerase inhibitors. The dose of drug in chemotherapy is correlated with toxicity, side effects and many other factors. There is a direct correlation between dose of drug and the percentage of cells killed in chemotherapy [8]. Therefore, the toxicity and side effects are considered in this study for drug dose scheduling in chemotherapy [7], which is the main interest of this research.

In chemotherapy treatment, the quantity of dose depends on the type of drugs. For determining the appropriate dose of chemotherapeutic, some oncologists use body weight, and others use body surface area. Besides some use the actual weight of patients, and others use the ideal body weight for the patient's height and frame. These dissimilarities affect considerable differences in calculated dose or dose intensity [9]. In the last 50 years, with the relation to the patient's body surface area (BSA), most cytotoxics have been suggested, and this surface area is calculated by their height and weight. But this is not used for all types of cancer [10].

Maximum tolerated doses of chemotherapy are being used to the patients by the doctors at the outset to kill the most tumor cells and hope to eliminate the tumor before resistance appeared. According to

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the theory of cancer evolution, high doses of drug therapy not only cause significant side effects, but also remove the proliferation resistance of competitive drug-resistant tumor populations. High doses also accelerate the proliferation rate. This phenomenon is called competitive release [11,12]. In many cases, the inaccurate body surface area-dosing found inconvenient and became important to find methods for more accurate dose calculation, which should be based on the known drug elimination processes for cytotoxic chemotherapy [13]. It is observed by the early study of the National Cancer Institute in Milan-patients who have lymph-node-negative early-stage breast cancer and were being randomized to undergo systemic adjuvant chemotherapy with CMF (cyclophosphamide, methotrexate, 5-fluorouracil) received more than 85% of the normal dose had better cancer reduction and recurrence rate than patients who received normal dose [14]. By changing some factors: administered dose, time interval of administration, or both, dose intensity can be increased or decreased [15].

For minimizing the toxicity of the drug and predicting the growth of the tumor, many mathematical models have been reported in recent years focusing on cancer chemotherapy [16,17]. The main suboptimal problems in cancer chemotherapy are doses, drugs, and schedules [18]. Some attractive efforts for optimizing scheduling problems are discussed in the literature review section which focused on maximum tolerated dosing. But none of them considered present clinical practice, which is weight-based dose calculation along with experts' opinions. In many cases, clinical people do not understand these computational models for drug dose calculation, as a result, none of them are useful for them.

In this present research, a clinically relevant fuzzy system model for chemotherapy drug dose scheduling is proposed. In real-world situations, fuzzy logic allows decision makers to analyze the system from approximate information and convert linguistic variables into mathematical variables, even in ambiguous situations [19,20]. The fuzzy expert system uses linguistic variable management system whose primary purpose is to provide expert advice in specific situations, and may improve the accuracy and efficiency of medical practice [21,22]. In the proposed system, Fuzzy Expert System −1 is developed based on the Fuzzy System where experts' opinions are incorporated to determine primary drug doses, where competing objectives are considered. To determine the dose adjustment percentage, another Fuzzy Expert System, FES-2, is developed considering calculated dose, which is clinically calculated using patient's weight, and experts' opinion. Combining the outputs of these two Fuzzy Expert Systems, final chemotherapy drug dose schedule is generated. To determine and observe chemotherapy drug dose related parameters, we used a growth model. The amount of drug calculated using BSA is an approximation based on the body height and weight. Though deterministic, fuzzy system is capable of reasoning better with such approximated or estimated information where direct measurement is not possible.

2. Literature review

Many of the current chemotherapy drug dose scheduling models hold high potential and some important methods can be divided into three phases, which are described below.

One of the most important works is [23] that used differential equations to describe the drug scheduling models in the chemotherapy for treatment of cancer. When this control optimization is performed by subjecting the constraints on the drug concentration ≤ 50 [23] and on cumulative drug toxicity $< 2.1 \times 10^3$ [23] and drug delivery ≥ 0 where the final/interval time was 84 days. The works by Skipper [24], Crowther [25], and Goldie & Coldman [26] proposed three-point constraints by the fact that the majority of the chemotherapy fails because of the drug resistance as the drug-resistant cells will increase as the duration of tumor burden increases. The cancer chemotherapy three-point constraint is focused to achieve a 50% reduction of the tumor size in every three weeks and minimize the drug-resistant cell's potential emergence. The constraints are: $x1(21) \geq \ln(200)$, $x1(42) \geq \ln(400)$ and $x1(63) \geq \ln(800)$ [27–30]. Considering these three-point constraints, Martin and Teo's [31] performance index I was 16.836, and the final tumor size of $N = 4.878 \times 10^4$ cells. In the studies, Bojkov [29] used the direct search optimization and obtained 17.223 ($N = 3.31 \times 10^4$). Luus et al. [30] also used direct search optimization and obtained 17.476 ($N = 2.57 \times 10^4$), Tan et al. [27] used evolutionary computation and obtained 17.99 ($N = 1.53 \times 10^4$), Floares et al. [28] used adaptive neural networks to maintain the drug dose regimen and obtained 18.22 ($N = 1.22 \times 10^4$).

In contrast, some researchers think that the overall efficiency and effectiveness of cancer chemotherapy cannot be improved by the three-point constraints [27–30,32]. They only consider the drug toxicity. It simplifies the rules by excluding the constraints like: $x1(21) \geq \ln(200)$, $x1(42) \geq \ln(400)$ and $x1(63) \geq \ln(800)$. Carrasco and Banga [33] used this line of research and obtained 17.742 as performance index I ($N = 1.97 \times 10^4$ cells).

In recent years Taguchi immune algorithm (TIA) helps the physicians selecting an efficient period for the drugs administration. It treated the drug schedule as a high dimensional and multimodal optimization problem [34] which improved the overall effect on the simulation but the toxicity was 100 [34] on most of the dosing dates which is the maximum limit. Thus, a patient with high toxicity tolerance uniquely can have a better schedule with this algorithm whereas others may suffer [34]. Another approach by Wang [35] was to use the memetic algorithm and general cell cycle algorithm with taking drug resistance, drug combination, and cell cycle into account. In this study, they formulated an algorithm that treats this problem as a nonlinear optimization problem and proposed a feasibility-based local search with a memetic algorithm. This approach does not have a regular cycle as the clinic has. This means the drug regiment set by them has no cycle like three weeks or four weeks. El-Garawany [16] used an embedded fuzzy controller to balance the trade-off between the cancer cell, toxicity, and drug, using Mamdani inference and hardware in the loop simulation study. It has a performance index I of 25.5099 ($N = 8.34$).

A similar but updated work using fuzzy was proposed by Karar [17]. It was specific for intravenous anti-cancer drug delivery that used invasive weed optimization (IWO) along with intuitionistic fuzzy sets. A mathematical patient model was used to evaluate this model and its performance index I was 27.63 ($N = 0.806$). Among recent studies, reinforcement learning [36,37], evolutionary genetic algorithm (GA) [38], metronomic chemotherapy [39], and other mathematical models [40,41] were implemented to deal with cancer and chemotherapy.

Recently, several fuzzy modular systems that take into account various adaptive architectures have been described. The modular fuzzy system was applied in [42] to predict defects in the agile manifesto, where the explosion of fuzzy rules was controlled using modular fuzzy concepts adopted from [43]. Kajornrit et al. in [44], predicted the rainfall by implying the modular concept for creating twelve monthly FIS sub-models. The historical data has been examined at both seasonal and non-seasonal levels at the same time which has produced better prediction accuracy was the advantage of the modular concept. Further, wheelchair was stabilized in [45] by using modular fuzzy controlling system, where two different fuzzy system controller controls the torques, lifting, and stabilization of the chair to provide optimized fuzzy rule bases.

3. Cancer cell growth analysis

In this research, a growth model is used for detection of cancer cells and its constraints formula is used for helping dose scheduling. Mainly the amount of dose is controlled by the fuzzy system. The output of growth model is input into both the FES, where FES-1 receives only the number of cancerous cells and toxicity of patient's body and FES-2 receives input as number of cancerous cells, toxicity of patient's body and calculated dose using weight of the patient.

3.1. Martins model for determination of cancer cell and toxicity

Martin's model is used as a growth model in our research to observe different parameter of a cancer patient. This model defines the effect of toxicity and doses concentration on the cancer cells and establishes a relationship among them using equations also calculates the number of tumor cell at a certain time. The equations are [23,31]:

$$\dot{C}(t) = D(t) - \lambda C(t) \tag{1}$$

$$\dot{N} = \frac{1}{\tau g}\left[\frac{\ln \frac{\rho g}{N_0}}{n\frac{\rho g}{2N_0}}\right] N(t) \ln\left[\frac{\rho g}{N(t)}\right] - K_{eff} C_{eff}(t) N(t) \tag{2}$$

$$C_{eff}(t) = \left[C(t) - C_{th}\right] H\left[C(t) - C_{th}\right] \tag{3}$$

$$H\left[C(t) - Cth\right] = \begin{cases} 1 & if\ C(t) \geq C_{th} \\ 0 & if\ C(t) < C_{th} \end{cases} \tag{4}$$

$$\begin{cases} C(0) = C_0 = 0 \\ N(0) = N_0 \\ \dot{T}(t) = C(t) - \eta T(t) \end{cases} \tag{5}$$

Where, $C(t)$ is plasma drug concentration, $D(t)$ is the amount of intravenous infusions of the drug, λ is the elimination kinetics rate, ρg and τg, describe the cancerous cells proliferate in a Gompertzian fashion, N_0 is the initial number of cancer cells, $N(t)$ is the number of cancer cells after every treatment cycle, $C_{eff}(t)$ is the effective drug plasma concentration, Cth is the minimum therapeutic concentration.

According to this equation, the initial drug concentration C_0 is considered as 0 and Cth controls the lower amount of drug concentration. $H\left[C(t) - C_{th}\right]$ is the Heaviside step function helps to calculate effective drug concentration [23,46]. K_{eff} is the constant that helps to evaluate the drug effect by multiplicity with number of cancer cells and effective drug concentration. The toxicity level is defined after infusion of drugs. For measuring toxicity η is a constant.

3.2. Constraints for dose schedule

a. As drug dose contains relationship with other factors, a limitation procedure needs to apply over a particular range of dose level, as follows [47]:

$$D_{th} \leq D(t_i) \leq D_{\max}$$

$$\text{or } D(t_i) = 0, \quad \forall i \in \{1, 2, \ldots, m\} \tag{6}$$

Here, t_i is the i_{th} dosing time and m is the final dosing point and D_{th}, $D_{\max}$ are the lower and upper bounds of the therapeutic dosing range. Since, in the present research Fixed Interval Variable Dosing (FIVD) scheme is used, $D(t_i)$ will be zero in those days when chemo dose is not applied and during scheduled dates, dose ($D(t_i)$) will be within the range of D_{th} and $D_{\max}$.

b. There is an upper limit of toxicity for human that can be tolerated. During the whole period of chemotherapy treatment, the maximum toxicity needs to be remained under the $T_{\max}$. Researcher suggest that the toxicity should not exceed $T_{\max}$ during the treatment [48]. If the last cycle is given with a final time t_f then $T(t)$ should be

$$T(t) \leq T_{\max} \text{ and } \forall t \leq t_f \tag{7}$$

c. Researchers suggested that total drug concentration must be remained below the cumulative drug concentration and total drug concentration, C_{Tot} is calculated by integrating drug plasma concentration over the treatment interval [47].

$$C_{Tot} = \int_1^{t_f} C(t)dt \leq C_{cum} \tag{8}$$

d. It is the obvious demand to reduce the number of tumor cells of a patient. So, it is an efficacy constraint that the number of tumor cells need to be remained less than the initial condition during the treatment [47].

$$N(t) \leq N_0 \text{ and } \forall t \leq t_f \tag{9}$$

Table 1 shows the values of constants used in our research, which are taken from the case study by Martin [23,31,46].

3.3. BSA calculation

Estimation of BSA can be done applying a number of different methods such as formulas, slide rulers, or nomograms among which two equations are most commonly used equations [49]. Mosteller [50] used body height and weight for BSA.

$$BSA\ (\text{m}^2) = \frac{\sqrt{height\ (\text{cm}) \times weight\ (\text{kg})}}{60} \tag{10}$$

Also weight base formula is used in calculation of BSA as

$$BSA\ (\text{m}^2) = \frac{weight\ (\text{kg}) \times 4 + 7}{90 + weight\ (\text{kg})} \tag{11}$$

The most recent measurement of height and weight are used in Eqs. (10)–(11). The dose is calculated by multiplying the amount of dose administered per cycle by BSA [10,51].

3.4. Performance index calculation

x_1, a transformed variable which is inversely related to the tumor mass N, defined as

$$x_1 = \ln(N * 10^{12}) \tag{12}$$

To determine the maximum effectiveness of chemotherapy drug dose scheduling performance index I can be calculated as follows [17,46,52]:

$$I = x_1(t_f) \tag{13}$$

Where, $x_1(t_f)$ means value of x_1, calculated from Eq. (12), at treatment time t_f when tumor mass is N. In the present study the final treatment time t_f is considered as 84 days.

4. Modular Fuzzy system for dose scheduling

The architecture of the proposed modular fuzzy system is shown in Fig. 1. The modular fuzzy system comprises two fuzzy systems with different inputs–output and rule-bases placed in a hierarchy. FS-1 calculates an initial dose and FS-2 determines the percentage of required change in initial dose considering experts' opinion and present clinical dose calculation practice. After combining these two outputs from FS-1 and FS-2, Dose Level is feed in to dose schedule generator, developed as per clinical practice, which gives the final dose schedule. This dose is applied into the growth model (Martin's model), to observe the effect of applied dose in to a cancer patient's body. The response of the body (number of cancer cells and toxicity) is continuously feedback into the developed fuzzy systems to generate the next best dose for the patient.

In this research, the fuzzy system is integrated with a growth model to observe the numerous cancer cells, toxicity and changed doses. Fuzzy system maintains the uncertainty of the inputs and growth model helps to calculate the numerous tumor cell and toxicity. A dose scheduler is also helps to reduce the complexity. Considering patient's weight along with tumor size and toxicity while calculating and further calibrating the dose for chemotherapy will result in destroying more cancerous cell, in other words, better outcome.

Table 1
Description and values of parameters used in Martins model.

Parameter	Description	Value	Units
τ_g	First doubling time of the cancer tumor during exponential growth	150	days
ρ_g	Plateau population of cancer cells without treatment	10^{12}	Cells
N_0	Initial cancer cell population	10^{10}	Cells
K_{eff}	Fractional cell kill term for a highly effective drug	2.7×10^{-2}	$\frac{1}{days.[D]}$
λ	Decrease in concentration of drag per unit time	.27	$\frac{1}{days}$
η	Toxicity rate constant	.4	$\frac{1}{days}$
D_{th}	Threshold drag level	10	[D]
D_{max}	Maximum tolerable drug level	50	[D]
C_{cum}	Maximum tolerable drug exposure in plasma	4.1×10^3	[D].days
T_{max}	Maximum tolerable toxicity	100	[D]

4.1. Fuzzy modeling

Fuzzy modeling is a great solution where the system is complex and partially known and the inputs and output cannot be measured directly. Also, the inputs contain some level of uncertainty. In this research, Mamdani-type fuzzy inference system [53] is used in both fuzzy systems. Tumor size and toxicity are used as the inputs to the first fuzzy system and tumor size, toxicity and calculated dose are used as inputs to the second fuzzy system. Two fuzzy systems are used to calculate the final dose to be applied to the patient. The inputs and outputs of the two fuzzy systems are described next.

Tumor size: It describes the number of tumor cells. Tumor size distribution is very effective in cancer systematic therapy [54]. Which is a better predictor for calculated doses [55]. The overall tumor size of a cancer patient also affects the survival rate. We have considered the initial number of tumor cells (10^{10}) and then we take the input of tumor cells from the output of the growth model.

Toxicity: Toxicity has some characteristics that are trade off among other variables. It correlates with chemotherapy doses. Different doses build different type and amount of toxicity [56]. Human body can tolerate a certain amount of toxicity. Doses of chemotherapy decrease the number of tumor cells along with that the normal cells are also destroyed [57]. When the doses are increased, the numbers of tumor cells are decreased but toxicity increases. This is the limiting factor for infusion of drug doses.

Estimated dose with weight: It describes the dose which is calculated according to the body surface area (BSA) of the person for a certain time which is calculated using Eq. (11). Different medicines need different amounts of dose for every cycle. By multiplication of BSA with the amount of dose that is given for one cycle, is the result of calculated dose [8,51].

Dose: It is the output of the first fuzzy system. Tumor size and toxicity are used as input in this expert system. Trapezoidal and triangle membership function and optimized fuzzy rules are used to calculate dose in this fuzzy system.

Changed Dose: This is the output of the second fuzzy system. ChangedDose is calculated considering the input values of tumor size, toxicity and calculated dose. It describes the percent of increase in dose calculated from FS-1, while considering the patient's weight.

Both the fuzzy systems are designed employing Mamdani-type inferencing, general fuzzification [58,59], appropriate choice for defuzzification method [60], fuzzy rule-base developed using experts' opinion from the domain and through calibration of parameters in several runs and patterns.

4.2. Fuzzy system 1

Fuzzy system 1 has two inputs: tumor size (i.e. the number of cancerous cells) denoted as TS and toxicity of patient's body, denoted as TX, and one output as chemotherapy dose (primary dose) denoted as D. To determine the best and suitable combination of membership function, (in terms of performance of the system, tumor size at the end of the treatment and the performance index), different types and combination of Membership function is experimented. According to our experiment the best suited Membership functions (MFs) which are used in our proposed method for TS, TX and D are described in the following sections (see Figs. 2(a), 3 and 4).

Table 2(a)
Parameters of Bell-shaped MFs for tumor size TS.

MFs	MF Parameters
Very Small (VS)	[0.8242 3.278 −2.5]
Small (S)	[0.8242 3.278 5.551e−17]
Medium (M)	[0.8242 3.278 3]
Big (B)	[1 2.5 6.5]
Very Big (VB)	[1 2.5 10]

Table 3
Parameters of Gaussian and triangular MFs for TX.

MFs	Parameters
Very Low (VL)	[13.89 0.15]
Low (L)	[0 30 60]
Medium (M)	[30 60 90]
High (H)	[60 90 120]
Very High (VH)	[2.421 117.2]

Tumor size (TS): Taking into account a slight chance of increase in tumor population, its practical range for tumor cell number can be considered 0 to 10^{11} [23,31,46]. However, in this study, the number of tumor cell is calculated from model. So, fractional values like 0.24 or 1.3×10^{-4} can be possible. We set the range for tumor cell number 10^{-3} to 10^{11}. For convenience in representation, original TS is transformed in logarithmic form. Taking the logarithm of 10^{-3} gives −3 and logarithm of 10^{11} gives 11. Now the transformed range for TS becomes [−3, 11]. Five bell-shaped MFs for tumor size are used for TS = {VS, S, M, B, VB}. Bell-shaped membership function is defined by three parameters [*p, q, r*], the parameters are defined below:

p is the half width,
q (along with *p*) controls the slopes,
r is the center of the associated MF,

The parameters of the MFs for TS are given in Table 2(a).

Toxicity (TX): Toxicity level per day is expressed as linguistic variable "Toxicity". The considered range is from 0 to 105. Though the maximum allowable toxicity is 100 per day [23,31,46], to identify the unacceptable drug dose values maximum range is slightly elevated to 105. Five MFs are used for toxicity TX = {VL, L, M, H, VH}. Gaussian MFs are chosen for VL and VH and triangular MFs are chosen for L, M, and H. The parameters of the MFs for TX are given in Table 3.

Dose (D): Output variable is expressed as linguistic variable "Dose". It characterizes dose level per day. The considered range is 10 to 50, where 10 being the threshold drug concentration [23,31,46]. Seven MFs are used for D={VVL, VL, L, M, H, VH, VVH}. Triangular MFs

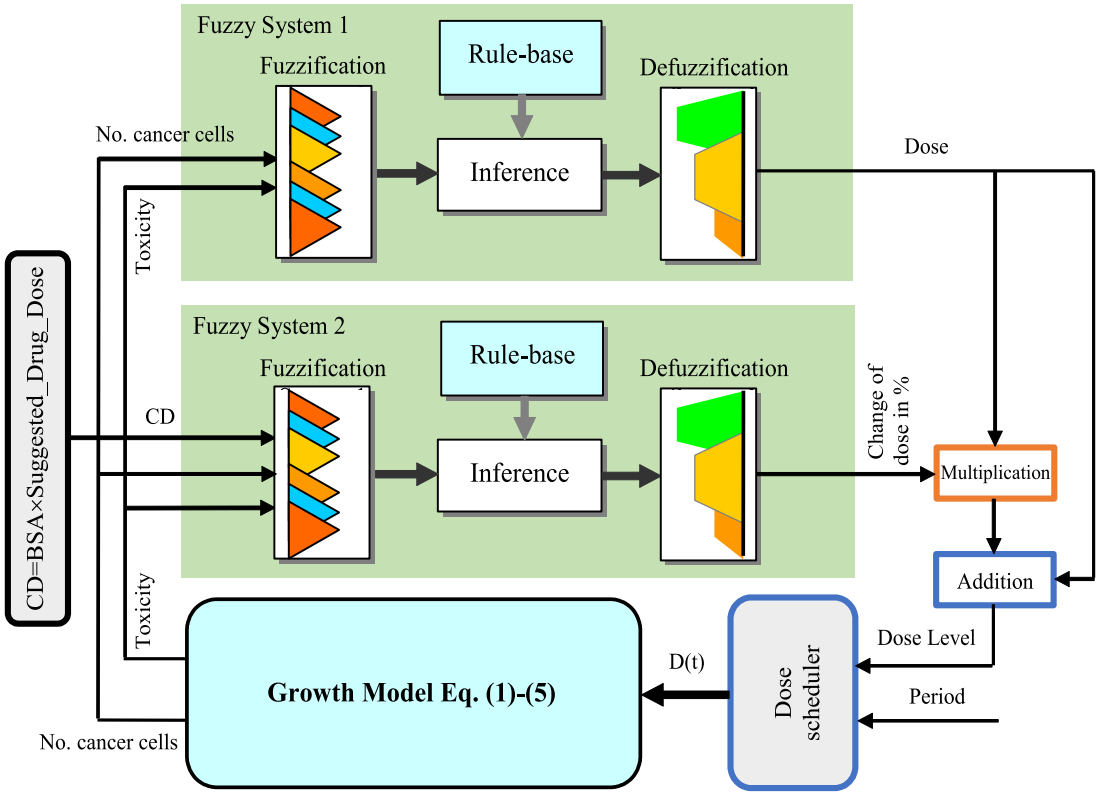

Fig. 1. Architecture of proposed Modular FES-based Model.

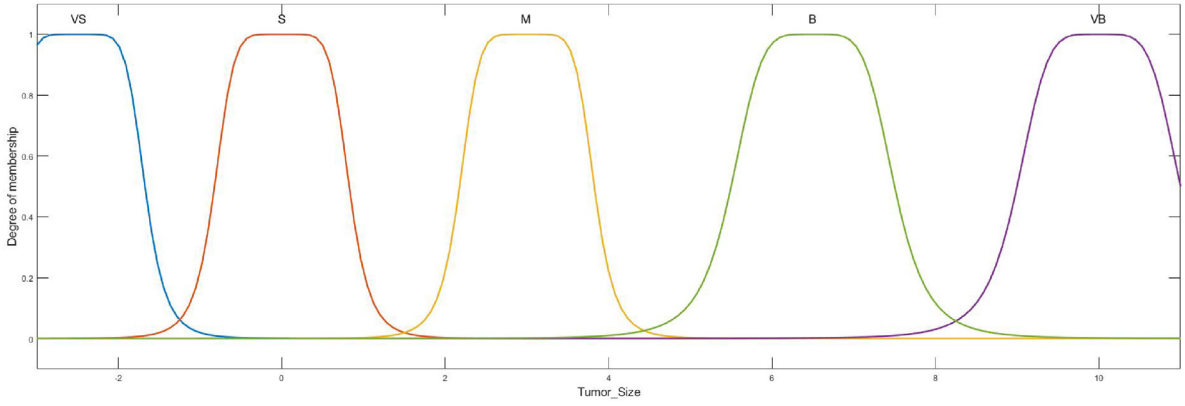

Fig. 2(a). Five MFs for tumor size.

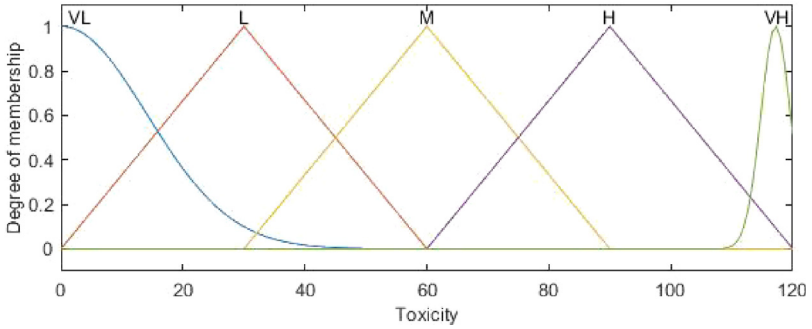

Fig. 3. Five MFs for toxicity.

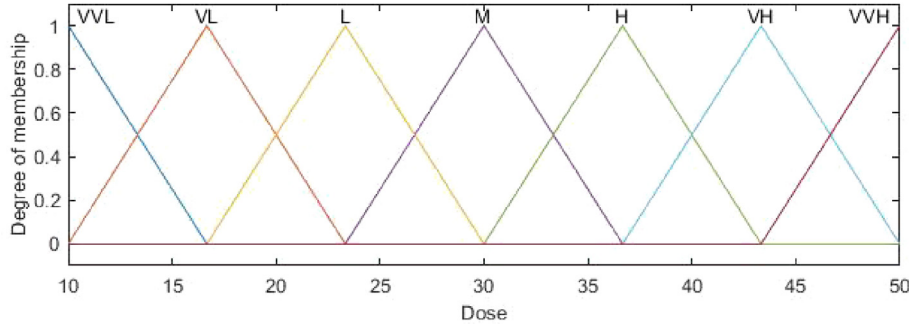

Fig. 4. Seven MFs for Dose.

Table 4
Parameters of triangular MFs for D.

MFs	Parameters
Very very Low (VVL)	[10 10 16.67]
Very Low (VL)	[10 16.67 23.33]
Low (L)	[16.67 23.33 30]
Medium (M)	[23.33 30 36.67]
High (H)	[30 36.67 43.33]
Very High (VH)	[36.67 43.33 50]
Very very High (VVH)	[43.3 50 50]

TS	TX				
	VH	H	M	L	VL
VS	VVL	∅	∅	∅	∅
S	VVL	VVL	VL	L	M
M	VVL	VL	L	L	H
B	VL	L	M	H	VH
VB	L	M	H	VH	VH

Fig. 5. Rule base for FES-1 in table format.

are chosen for all MFs. The parameters of the MFs for D are given in Table 4.

Rule-base: The fuzzy rule-base is constructed using expert knowledge. For the five MFs for both TS and TX, the rule-base should contain 25 rules for all possible combinations of inputs and output variables. Due to insufficient work-space coverage, some rules will never fire. Considering the model constrains (Eqs. (6)–(9)) and through trial and error, the number of rules is minimized to 21. The fuzzy system 1 with the two inputs (TS and TX) and one output (D) has 21 rules, which are presented in table format in Fig. 5. It shows the impact of Dose on the primary concern which is tumor size and how it gets reduced while keeping the toxicity below the maximum threshold.

4.3. Fuzzy system 2

Fuzzy System 2 has three inputs: tumor size TS, toxicity of patient's body TX, and calculated dose CD. The fuzzy system provides increase/adjustment of chemotherapy dose in percent as output denoted as I. The MFs for TS, TX, CD and I are described below:

Table 2(b)
:Parameters of MFs for tumor size TS.

MFs	Type	MF Parameters
VS	Gaussian	[2.2 −1.6]
S	Triangular	[−0.5 2.25 5]
B	Triangular	[3 5.75 8.5]
VB	Gaussian	[1.2 9.85]

Table 5
Parameters of triangular MFs for CD.

MFs	Type	Parameters
LowDose (LD)	Trapezoidal	[0 0 165 180]
NormalDose (ND)	Triangular	[165 180 202]
OverDose (OD)	Triangular	[184 202 216]
VeryOverDose (VOD)	Trapezoidal	[200 245 300 300]

TS: In fuzzy system 2 the TS is divided into four MFs within the range [−3, 11]. The four MFs are TS = {VS, S, B, VB} (see Fig. 2(b)). The parameters of the MFs for TS are given in Table 2(b).

TX: The input TX is the same as in fuzzy system 1. Five MFs are used for TX = {VL, L, M, H, VH} (see Fig. 3).

CD: In Clinics, dose is generally calculated as product of BSA with the suggested amount of drag [61].

$$\mathrm{CD} = \mathrm{BSA} \times \mathrm{Suggested\_Drug\_Dose} \tag{14}$$

Suggested drug dose varies from drug to drug, as per the drug guideline. Here, drag amount is considered 100 mg/m^2 for a specific type of drag like Epirubicin. Considering Mosteller rules obese adults' BSA is 2.25 ± 0.21 m^2 [62]. In the present study, fixed interval variable dose (FIVD) scheme is used. So, at a certain interval drug dose will be applied to the patient and in other days no drug will be applied, that is the amount of drug dose will be zero. So, the range of the third input, calculated dose CD, is considered as 0 to 300. This interval will be changed if a different drug is used drug amount is changed as per the drug guideline. Four MFs are used for CD= {LD, ND, OD, VOD} (see Fig. 6). The parameters of the MFs for CD are given in Table 5.

Percent dose I: Output variable for percent of increase in dose is expressed as linguistic variable "Percent dose I". Here, we calculated the changed dose according to the input value Tumor size, Toxicity and Calculated dose using patient's weight. It describes the percent of increase in dose calculated from fuzzy system 1, while considering the patient's weight, measured in every chemo cycle. According to Skipper [63], it is observed that 20% of dose reduction can reduce the cure rates by 50% or more [15]. Considering Bonadonna-et-al.s' [14] observation, in our experiment we considered the range for "Percent dose I" 0% to 80%. Four MFs are used for "Percent dose I", I = {N, LI, IN, VI} (see Fig. 7). Trapezoidal MFs are chosen for *N* and VI and triangular MFs are chosen for LI and IN. The parameters of the MFs for I are given in Table 6.

Rule-base: The number of rules of a fuzzy system increases with number of inputs and their MFs. Processing huge number of rules of

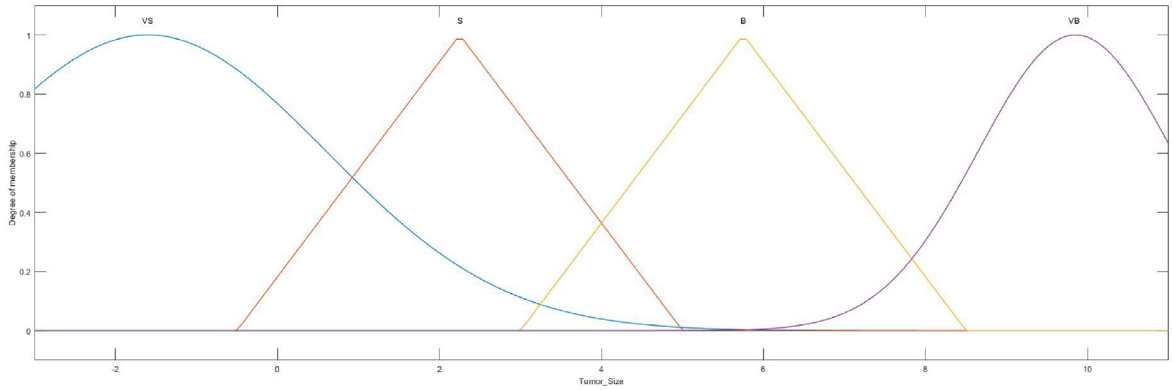

Fig. 2(b). Four MFs for tumor size.

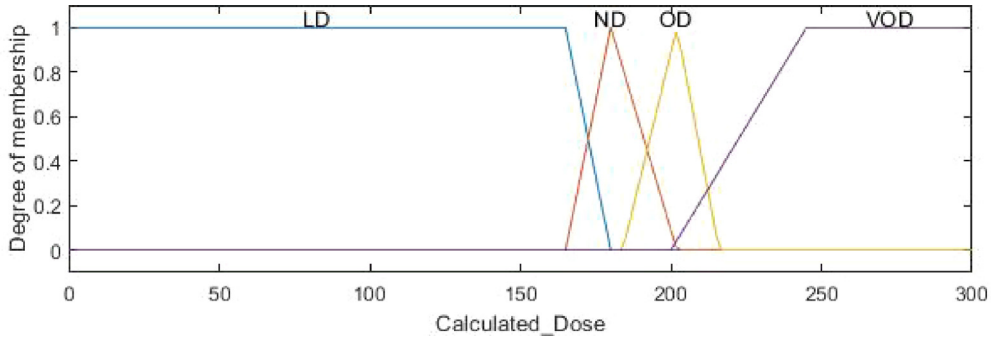

Fig. 6. Membership functions for Calculated_Dose.

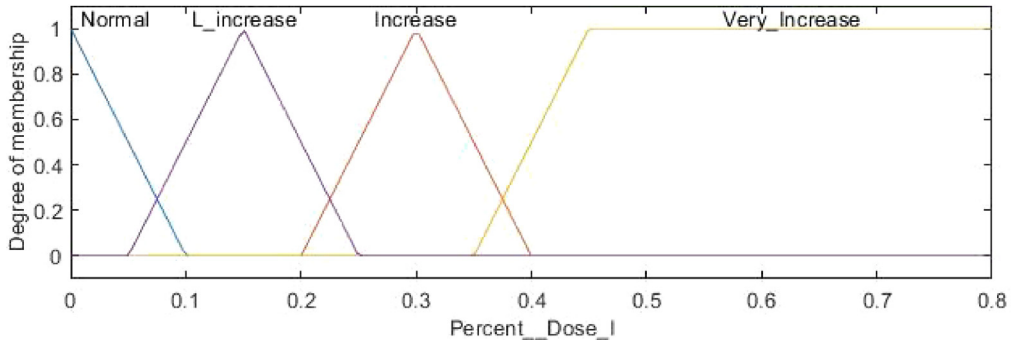

Fig. 7. Membership functions for Percent_Dose_Increase.

Table 6
Parameters of MFs for percent_dose_I.

MFs	Type	Parameters
Normal (N)	Trapezoidal	[0 0 0 0.1]
Low Increase (LI)	Triangular	[0.05 0.15 0.25]
Increase (IN)	Triangular	[0.2 0.3 0.4]
Very_Increase (VI)	Trapezoidal	[0.35 0.45 0.8 0.8]

fuzzy systems is time consuming, which is detrimental to performance. Therefore, the reduction of rules for fuzzy systems is seen as an objective. For three inputs TS, TX and CD with 4, 5 and 4 MFs respectively, the number of rules becomes 80 (4 × 5×4=80) for the fuzzy system 2 in Fig. 1. A variety of approaches are available to reduce the number of rules for a three-inputs and single output fuzzy system [53]. The three-inputs single-output fuzzy system can be decomposed into a two-inputs fuzzy system in parallel with a fuzzy gain or a single-input fuzzy system as shown in Fig. 8(a)–(b). The outputs are summed to produce the final output percent dose I. In 8(a), a fuzzy system with two inputs {TS, TX} is implemented in parallel with a fuzzy gain for CD∈{0,300} where K is a gain factor to be tuned. For 8(a), K= .035 is considered, after tuning it to find the optimal performance of the system. This implementation requires 20 rules. In 8(b), a fuzzy system with two inputs {TS, TX} is implemented in parallel with a single input {CD} fuzzy system. This implementation of decomposed fuzzy system requires 24 rules (4 × 5+4=24). These two decomposed versions of fuzzy systems are implemented, evaluated and compared with the optimized three-inputs fuzzy system (see Figs. 9 and 10).

In case of three-inputs fuzzy system, the initial 80 rules, we get, in general, are generated from all combinations of fuzzy sets of all inputs and output of the fuzzy system. But expert knowledge following the clinical practice, as followed, suggests that some cases (some rules in fuzzy systems, generated initially) hardly/never appear as far as the disease, treatment, drugs used and physiological conditions of patients are concerned. To devise/develop a generalized procedure to optimize rule base, model constraints, as used in this work and listed in Eqs. (6)–(9) are used. It is to be noted that the constraints, as listed in Eqs. (6)–(9) and imposed on the model are consistent with clinical practice,

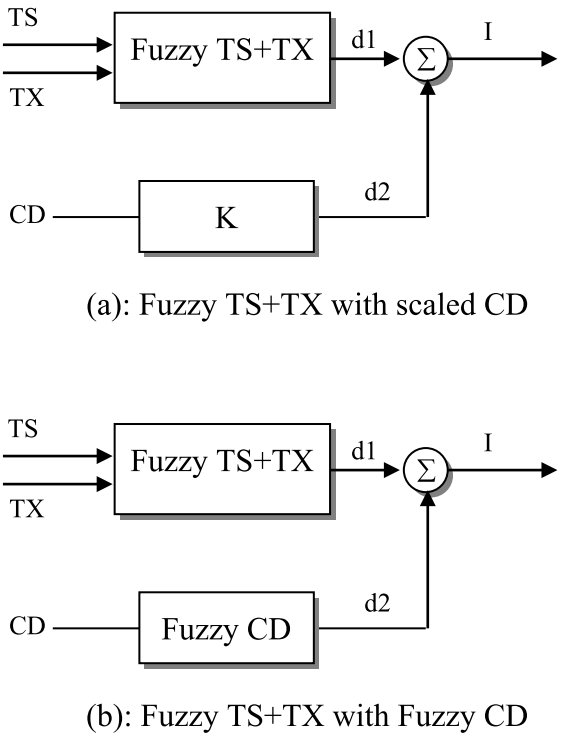

Fig. 8. Two different implementations of three-inputs and single output fuzzy systems.

such as, maximum allowable drug dose, maximum toxicity, tumor size, drug concentration at plasma etc.

After optimization the rules are stated as follows:

1. If TS=VS & CD=LD then I=N
2. If TS=VS & CD=ND then I=LI
3. IF TS=VS & CD=OD then I=IN
4. IF TS=VS & CD=VOD then I= IN
5. IF TS=S & TX=VL & CD=LD then I=N
6. IF TS=S & TX=VL & CD=ND then I=LI
7. IF TS=S & TX=VL & CD=OD then I= IN
8. IF TS=S & TX=L & CD=LD then I=N
9. IF TS=S & TX=L & CD=ND then I=LI
10. IF TS=S & TX=L & CD=OD then I= IN
11. IF TS=S & TX=M & CD=LD then I=N
12. IF TS=S & TX=M & CD=ND then I=N
13. IF TS=S & TX=M & CD=OD then I= IN
14. IF TS=S & TX=H then I=N
15. IF TS=S & TX=VH then I=N
16. IF TS=B & TX=VL then I=N
17. IF TS=B & TX=L then I=N
18. IF TS=B & TX=M then I=N
19. IF TS=B & TX=H then I=N
20. IF TS=B & TX=VH then I=N
21. IF TS=VB & TX=VL then I=N
22. IF TS=VB & TX=L then I=N
23. IF TS=VB & TX=M & CD=LD then I=N
24. IF TS=VB & TX=M & CD=ND then I=N
25. IF TS=VB & TX=M & CD=OD then I= IN
26. IF TS=VB & TX=H then I=N
27. IF TS=VB & TX=VH then I=N
28. IF TS=S & TX=VL & CD=VOD then I=N
29. IF TS=S & TX=L & CD=VOD then I=N
30. IF TS=S & TX=M & CD=VOD then I=N

The optimality criteria, J is defined using the performance index I (Eq. (13)), tumor size (TS) and Toxicity (TX)

$$J = f(I, TS, TX) \tag{15}$$

Subject to

$$\begin{cases} I > 0 \\ TS \approx 0 \\ TX < 100 \end{cases} \tag{16}$$

The first approach, shown in Fig. 8(a), satisfies all the constraints but has a lower value of I. But the second approach, shown in Fig. 8(b), does not satisfy the third constraint TX, where TX >100 (8(b) in Fig. 10,) even though it has the highest value of 35.64 for I (Table 7). The "Third Approach" satisfies all three constraints, where I=29.57, TS ~0 (0.1438) and TX <100 ("Third Approach" in Table 7 & Fig. 10). Therefore, among the three approaches, the "Third Approach" is optimal.

5. Simulation and results

The MATLAB/Simulink software and Fuzzy Logic Toolbox have been used to implement and perform simulation tests of our FES-based dose scheduler. In this study, the simulation time, 120 days is considered but to compare with other computational chemotherapy drug dose scheduling models up to 84th day's simulation output is considered. Table 1 describes all the parameters considered in our present research.

The main target of chemotherapy planning is to eliminating tumors as early as possible at the same time maintaining minimum toxicity. To provide efficient treatment while keeping the toxicity in limit, proper schemes of dose schedule should be chosen. To evaluate our proposed system for optimal dose generation, a clinically relevant dose scheme called fixed interval variable dose (FIVD) is used for interval between scheduled sessions and it is 14 days. The initial dose for the first day of treatment is considered as 40[D], which can be varied based on patient's weight and for the next cycle our proposed system will provide optimal dose considering weight, number of cancerous cells and toxicity of the patient's body.

We have used three streams of patient's weight considering increasing order of weight, decreasing order of weight and a mixed order where during treatment both increase and decrease of weight may occur. Table 8 describes three patterns of cancer patient's weight considered in this research, based on which the following arresting results (Table 10) are achieved. Only the first dose applied on the first day and next to all doses will be applied on two consecutive days as the 15th and 16th days. The increasing weight order for the patient starts from 90 and ends with 146 kgs. The decreasing weight order for the patient starts from 110 and ends with 64 kgs. And the mixed order contains both increasing, decreasing and unchanged weight order which start with 65 and ends with 80 kgs.

The time amongst two consecutive chemotherapy treatments is constant for the whole treatment phase in this fixed interval variable dose. Chemotherapy is given to patients on the first two days of every third week, with a 13-day break between treatments. Chemotherapy is only given nine times over the course of four months, with the first time being on a single day and the remainder of the time being on two consecutive days as shown in Fig. 11.

Different Membership functions have been experimented in both FES-1 and FES-2 along with various weight patterns. Table 9 shows that among various membership function combinations, the Bell-shaped-Gaussian-Trapezoidal–Triangular combination performed better than the others and this combination is implemented in our system.

One of the main goals of chemotherapy treatment is to reduce malignant cells, as these cells might spread cancer to other major organs. The number of malignant cells is considered as 10^{10} before treatment begins, which is supported by other studies [31]. Fig. 12 depicts the reduction of cancerous cells during the whole treatment period, where one can easily identify the number of cells is almost

Table 7
Comparison among different optimization approach (Increasing weight pattern data on 84th day is considered).

Optimization approach	Number of rules	No. of tumor cell	Performance index
8(a)	20	~0 (1.6698)	27.12
8(b)	24	~0 (3.3186×10^{-4})	35.64
"Third approach"	30	~0 (0.1438)	29.57

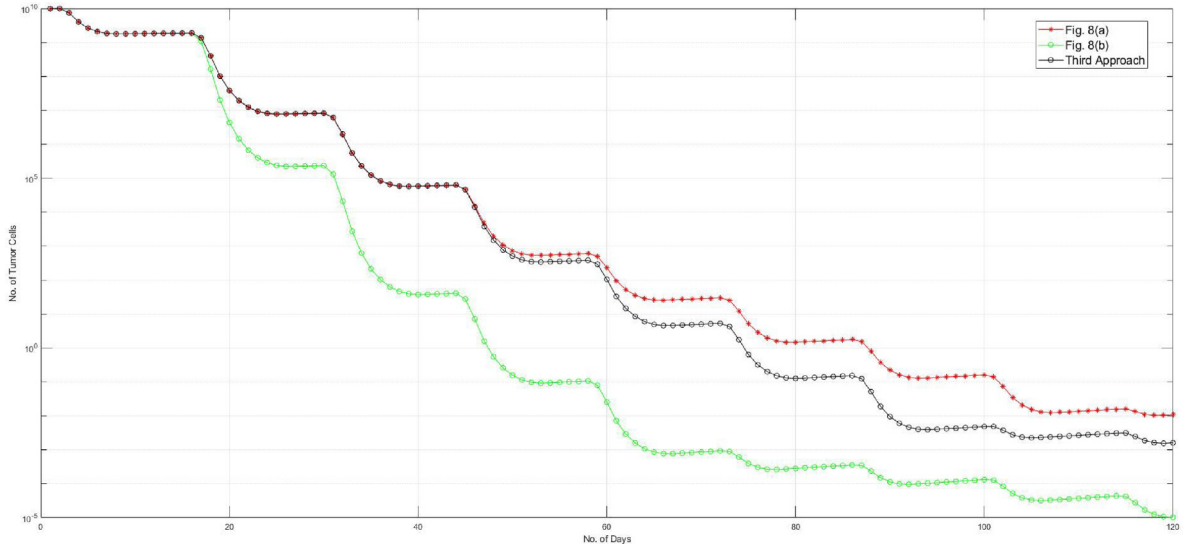

Fig. 9. Combined plot of the number of cancerous tumor cells, considering decomposed fuzzy systems in Fig. 8(a), Fig. 8(b) and "Third Approach".

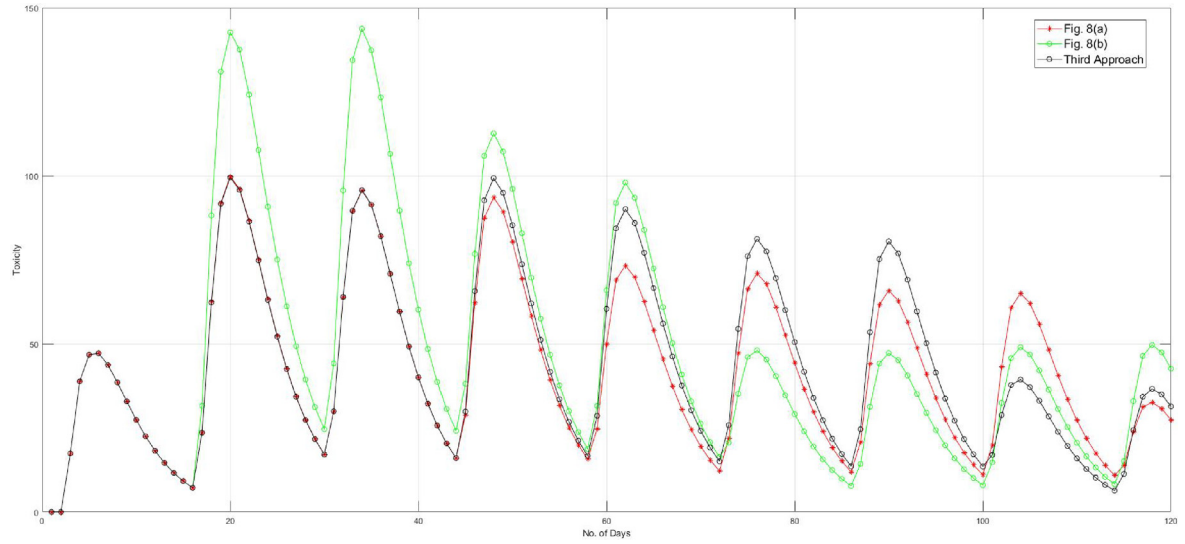

Fig. 10. Combined plot of Toxicity, considering decomposed fuzzy systems in Fig. 8(a), Fig. 8(b) and "Third Approach".

Table 8
Patterns of weight in kg (increasing order, decreasing order and mixed order).

Days	1	15–16	29–30	43–44	57–58	71–72	85–86	99–100	113-114
Increasing order	90	97	104	111	118	125	132	139	146
Decreasing order	110	104	98	92	86	80	74	68	64
Mixed order	65	70	75	80	86	80	74	80	80

zero within 84 days of treatment period. If we analyze Fig. 13, we can observe in the present context our proposed FES-2 suggests maximum 30% increase of drag dose over the dose provided by FES-1 during the treatment period. It may vary in other context.

In Fig. 13, the increase of dose in percent over the dose provided by FES-1 is depicted for three patterns of patient's weight.

This output is observed from FES-2, where input constraints is used as No. of cancerous cells, toxicities of patient's body and the calculated dose using weight, which is always followed in clinical practice. FES-2 provides a percent value, which indicates how much drag dose can be added over the calculated dose from FES-1. It suggests a high increase of dose on an average can be applied for increasing order of weight

Table 9
Results of different Membership functions combination for both FES-1 and FES-2.

Membership functions	Increasing	Decreasing	Random	Average	Performance index
Gaussian-trapezoidal	0.2542	0.4262	0.4308	0.3704	28.624
Gaussian	0.1952	0.3058	0.2977	0.2662	28.955
Gaussian-triangular	0.1468	0.2489	0.2407	0.2121	29.182
Gaussian-trapezoidal–triangular	0.1485	0.2427	0.2345	0.2086	29.198
Bell-shaped-Gaussian-Trapezoidal–Triangular	0.1438	0.2323	0.2229	0.1997	29.242

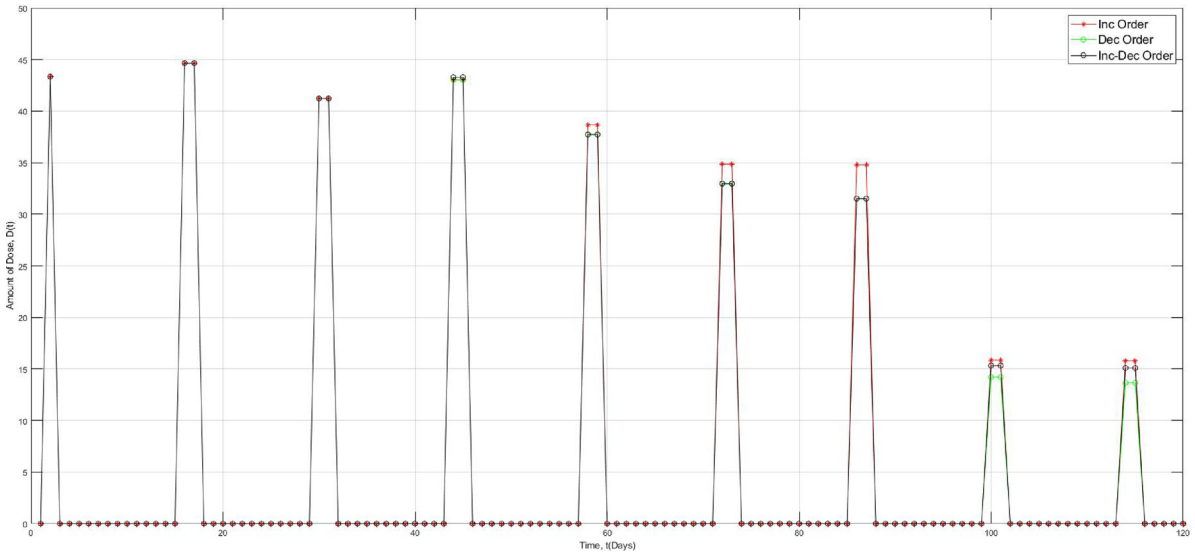

Fig. 11. Dose schedule for 120 days, considering increasing flow of weight, decreasing flow of weight and both increasing and decreasing flow of weight.

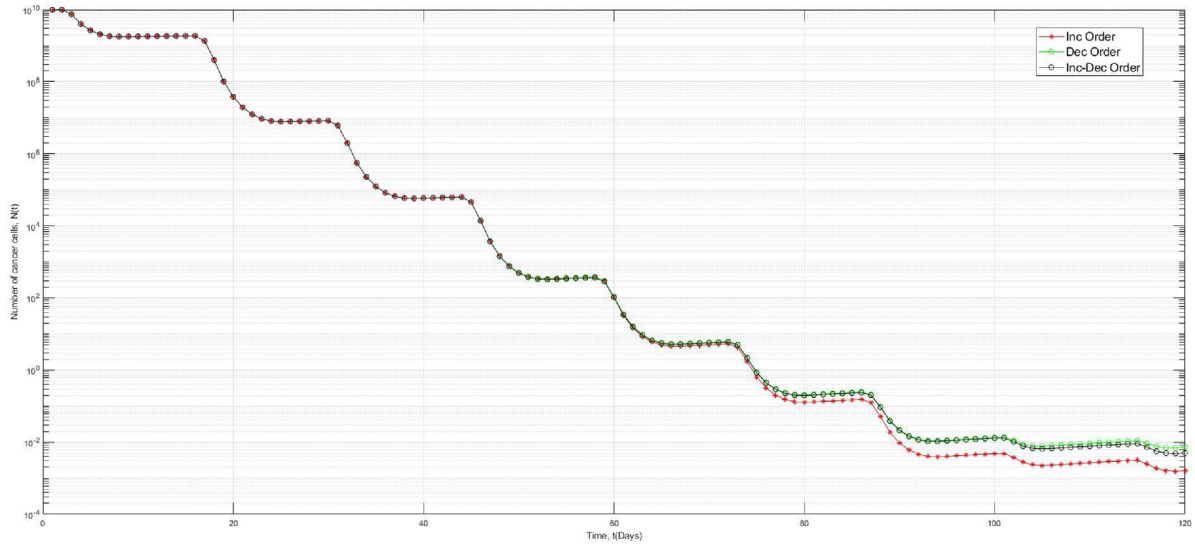

Fig. 12. Combined plot of the number of cancerous tumor cells for 120 days (interval 14 days), considering increasing flow of weight, decreasing flow of weight and both increasing and decreasing flow of weight.

flow. In decreasing weight flow, FES-2 suggests a high increase of dose in the second day for a large weight of patient. For increase–decrease flow of weight, FES-2 suggests a low increase of dose by considering both number of cancerous cells and toxicity in patients' bodies. For a patient, staying with high toxicities, the proposed system does not suggest a high increase of drag dose, which can be life threatening for a patient.

The toxicities for the three weight patterns corresponding drag dose scheduling are depicted in Fig. 14. For each three cases toxicity highly increased after the second dose was applied, but never crossed the maximum level of toxicity (100). The maximum level of toxicity (TX) is observed for the mentioned three cases, which is less than 100. It is worth to be noted that in all cases, toxicities remain under control and lower than the maximum limiting value.

A summary of the performance measure in response to three cases of weight pattern for proposed chemotherapy dose scheduling is shown in Table 10. The code schemes generated by the mentioned three cases successfully maintained the constraints described in the methodology section. Toxicity levels are kept below 100 and drag dose for a particular day never exceeds 50[D].

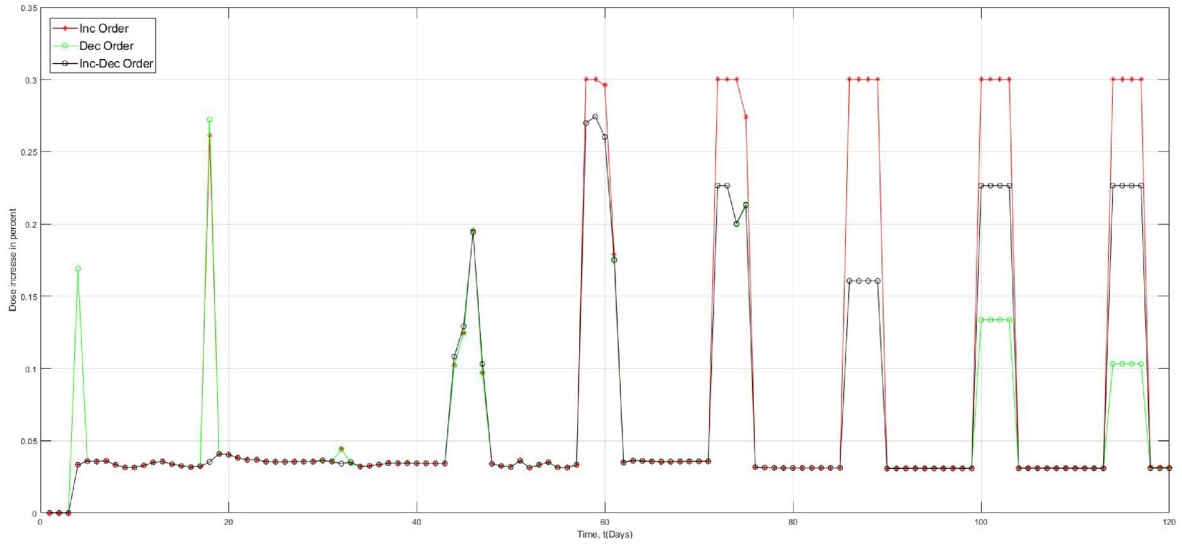

Fig. 13. Increase/Decrease of Dose in percent (%) over the dose calculated using No. of cell and toxicity.

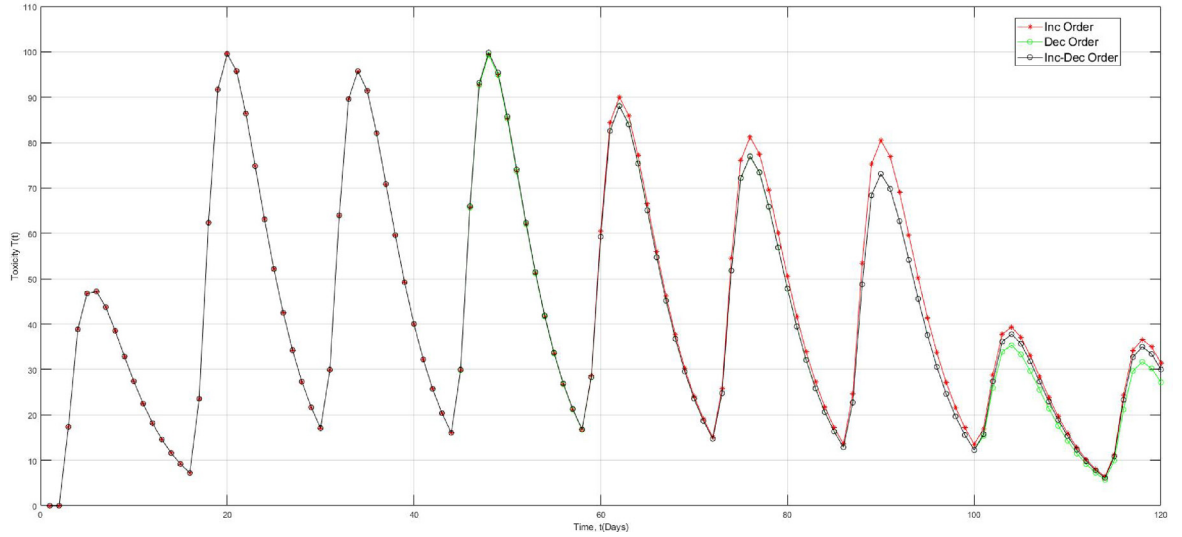

Fig. 14. Toxicity for 120 days (14 days of interval), considering increasing flow of weight, decreasing flow of weight and both increasing and decreasing flow of weight.

Table 10
Performance measure in response to three weight cases.

Case	Weight type	Drag dose	Toxicity	Dose increase (%)	Cum. drag. concentration	Initial tumor cell No.	Final tumor cell No.	Cell reduction
		Avg	Avg	Avg				
1	Increasing order	40.7430	48.4685	14.2059	448.1732	10^{10}	~0.1438	~100%
2	Decreasing Order	40.2296	47.8966	12.361	442.5253	10^{10}	~0.2323	~100%
3	Increasing-decreasing order	40.2730	47.9483	12.4614	443.0028	10^{10}	~0.2229	~100%

The cumulative drag concentration is lower than the maximum allowable level which is 4.1×10^3. The efficacy constraint is also maintained as the number of cells has never risen to a value above the initial number 10^{10}. The final tumor cell counts for case 1, 2 and 3 are respectively 0.1438, 0.2323 and 0.2229, which is the result till 84 days. In addition, after 120 days the number of tumor cells for the mentioned three cases is respectively 0.0017, 0.0075, 0.0052. The cell reduction is close to ~100% as compared to initial tumor cell number. By observing all three cases, it can be noted that the proposed methodology is effective in terms of cancer treatment. Further, the Maximum drug dose, Toxicity, and Dose increase for all 3 cases were 44.6474, 99.505, and 30% respectively. Cell reduction was close to ~100% for all cases and the initial number of cells was 10^{10}.

Table 11 compares the performance of the proposed approach with other optimal control methods in previous comparable studies, based on the performance index (Eq. (13)) and the ultimate number of malignant cells left after 84 days assuming normal toxicity sensitivity. Clearly, the proposed approach was successful in achieving the cancer treatment goal, as evidenced by the highest performance index of 29.242 and a tiny tumor size.

Table 11
Efficacy comparison with proposed method and existing methods of chemotherapy drag scheduling.

Drag schedule method	Performance index	Final number of cancerous cells
Tan et al. 2002 [27]	17.99	1.53×10^4
Tsai et al. 2013 [34]	24.74	18.0
Algoul et al. 2011 [48]	24.92	15.0
El-Garawany et al. 2017 [16]	25.51	~8 (8.34)
Khadraoui et al. 2016 [52]	27.56	~1 (1.078)
Karar et al. 2020 [17]	27.63	~1 (0.806)
Proposed method	29.242	~0 (0.1997)

6. Conclusion

The proposed system presents an optimal chemotherapy dose scheduling system using the modular fuzzy expert system. All monitoring doses were effectively applied throughout the treatment period, and the convergent result was a 100% reduction of cancer cells without violating treatment restrictions. More notably, the highest toxicity level during the treatment period remained below the maximum allowable value as previously reported and suggested by other researchers. Therefore, for clinical experiment, execution or clinical trials, the proposed dose regimen may be preferred. The proposed strategy clearly illustrates that, in addition to traditional methods, the proposed FES-based model for chemotherapy dose scheduling can assist oncologists/clinicians in planning optimal chemotherapy treatment scheduling. When compared to existing state-of-the-art models, our proposed optimization technique with well-defined limits produces highly satisfying results. Furthermore, personalized treatment plans can be created by altering model parameters based on the patient's physiological condition and tumor stage. The same design process can also be used to construct multi-drug or combination chemotherapy regimens.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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